UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

AUG 04 2005

MEMORANDUM

SUBJECT: Science Review in Support of the Registration of B2E-07 (EPA Registration No. 75318-T), Containing 2.800% (S)-Methoprene [Isopropyl (2E,4E,7S)-methoxy-3,7,11-trimethyl-2,4-dodecadienoate] [redacted], Chemical No. 105402) As Its Active Ingredient. Review of Product Chemistry Data, Efficacy Data and Toxicity Waiver Requests. DP Barcode 314532; MRID No. 46459201 through 46459208.

FROM: Angela L. Gonzales, Biologist
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511C)

TO: Mari Duggard, Regulatory Action Leader
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511C)

ACTION REQUESTED

B2E Biotech LLC requests registration of B2E-07 (EPA Reg. No. 75318-T), an end-use product (EP) containing 2.800% (S)-Methoprene [Isopropyl (2E,4E,7S)-methoxy-3,7,11-trimethyl-2,4-dodecadienoate], an insect growth regulator (IGR), as its active ingredient. The source [redacted] This product is intended to be sold in granular form for use to control mosquitoes, filter flies and non-biting midges in breeding areas. In support of registration, the registrant has submitted a Confidential Statement of Formula (CSF) dated 11/13/04, a proposed product label, product chemistry data in MRIDs 46459201-46459204, efficacy data in MRIDs 46459205-46459207, and acute toxicity waiver rationale in MRID 46459208.

~~**THE FOLLOWING PAGES CONTAIN CONFIDENTIAL BUSINESS INFORMATION**~~

RECOMMENDATIONS AND CONCLUSIONS

**Methoprene is exempt from the requirement of a tolerance in or on all food commodities when used to control insect larva. (40 CFR 180.1033)

Product Chemistry- ACCEPTABLE, pending correction of listed deficiencies below:

1. The percentage of the TGAI on the label must be consistent with that on the CSF. The registrant must change the percent of the TGAI on the label from 2.8% to 2.800%.

2. The registrant must change the spelling [redacted] on the CSF.

3. The Chemical Abstract Service (CAS) number on the CSF for the ingredient, [redacted] is incorrect. The registrant must change it from [redacted]

4. The registrant must explain the discrepancies between the differences in amounts of ingredients listed on the CSF, and the amounts used during the formulation process. The amounts of (S)-Methoprene, [redacted] differ on the CSF from those listed in MRID 46459203. Per the CSF and the formulation process, each batch produces [redacted] of B2E-07, so the amounts of ingredients listed on the CSF and used in the formulation process should be equal.

5. The registrant must clarify how [redacted]

Toxicology- ACCEPTABLE, pending registrant response to BPPD request for clarification of the listed item below:

1. The registrant must clarify if all fines (all respirable particles) are removed from the EP during the manufacturing process, and address the durability of the granules as to whether they may break apart easily during packaging, storage and use, which could possibly result in exposure to fine grains and their potential irritant effects.

Efficacy- UNACCEPTABLE, upgradable pending submission of requested information and BPPD subsequent review.

For all:

1. Label application directions indicate that the EP may be used "pre-hatch" (prior to flooding) or "post-hatch" (after flooding). However, product performance data were only submitted for post-hatch applications. The provided data do not support efficacy of pre-hatch application methods.

2. Based on the deficiencies noted below for each study submitted, there are inconsistencies between each study and label claims regarding length of control of mosquito populations and application rates. These discrepancies must be resolved.

3. Current application rates on the label are not applicable to all of the use sites (i.e.: tires, tree holes, ornamental ponds, etc.). For example, 3.0-7.0 lbs/A is not accurate to be used as an application rate for use in an animal watering trough.

MRID 46459205: SUPPLEMENTAL, no further data are required.

MRID 46459206: UNACCEPTABLE, upgradable.

1. The registrant must provide control data in order to validate the study.

If acceptable control data had been submitted:

1a. The submitted data demonstrate efficacy by means of percent inhibition of emergence (I.E.) of *Ochlerotatus melanimon* (pre- or post-hatch) at 2.5 pounds/acre (lbs/A) in sites with an average water depth of six inches for up to three days.

1b. Temperatures greater than 90°F were recorded at the site testing the EP against *Anopheles freeborni* and *Culex tarsalis*, which also dried out during the study. The registrant claims 100% I.E. at the sites, explaining that delayed development time is a secondary effect of (S)-Methoprene, therefore the larvae died by drying out before developing into pupae, and those that did develop died in the pupal stage. This cannot be verified without control data. If verified with control data, the submitted data demonstrate efficacy for the two species at 2.5 lbs/A with an average water depth of three feet for up to nine days.

2. Based on the experimental data (MRID 46459206) and data from literature submitted (MRID 46459205), it can be concluded that the EP is efficacious in controlling mosquito populations for up to nine days at indicated label rates. However, the length of control is not in accordance with label claims. Label rates currently establish control 30 to 80 days, depending on species of mosquito and application rate.

MRID 46459207: UNACCEPTABLE, upgradable.

1. OPPTS Guideline 810.3400 recommends a minimum of 95% population reduction for mosquito larvae. All but one treatment exhibited less (by greater than 10%) than the recommended percentage of reduction. The treatment that did provide a 95% inhibition of mosquito emergence exceeded the label application rate for the species on which the EP was tested. The registrant must alter the label application rates to reflect the results of this data.

2. The data submitted support control of *Aedes egypti* mosquito populations for up to seven days at 7.5 lbs/A, which is not in accordance with current label claims.

NOTE TO RAL:

1. All estuarine and marine sites, and sites where runoff can occur into estuarine and marine sites must be removed from the label. Submitted data on the TGAI do not support these sites.

2. The registrant has listed "other nuisance aquatic insect species" as target pests on one of the labels. Each target pest must be individually listed on the label, as this classification is too ambiguous.

3. Per OPPIN, the ingredient [redacted] However, this section number was not found in by the reviewer in the CFR, and also could not be found in 40 CFR 180.910 through 180.960. However, per OPPIN, this ingredient is used in products used in or on food that have already been registered by the Agency. The ingredient is also on the EPA List 4b, and is present at [redacted] of the composition of the EP.

STUDY SUMMARIES

Product Chemistry

B2E-07 is an EP intended to be used to prevent the emergence of adult mosquitoes. The active ingredient is 2.800% w/w isopropyl (2E,4E,7S)-11- methoxy-3,7,11-trimethyl-2,4-dodecadienoate (source material [redacted] The inerts are [redacted] The beginning materials were adequately presented and the certified limits were within OPPTS 830.1750 guidelines. The formulation process description did not explain [redacted] and the amounts of several ingredients were not consistent with the amounts specified on the CSF. No chemical reactions occur and no new impurities are formed during the manufacturing process. Preliminary analysis and enforcement analysis are not required. Physical/chemical properties were self-certified and are adequate.

Toxicology

The registrant requested waivers for mammalian toxicity testing requirements. Acute toxicity studies submitted for the [redacted] supported placement in Toxicity Category IV for each of the six-pack data requirements. The inert ingredients in B2E-07 are either on EPA List 4A or 4B, are regarded as GRAS by U.S. FDA, or are not of toxicological concern. [redacted] potential to have toxic/irritant respiratory effects, but in the EP, it is bound in a granular form which is not respirable. The registrant must clarify if all respirable particles are removed from the EP during the manufacturing process, and address the durability of the granules as to whether they may break apart easily during packaging, storage and use, which could possibly result in exposure to fine grains and their potential irritant effects.

With the exception of [redacted] low concentrations of the inerts in the formulation are not expected to have irritant effects.

Efficacy
MRID 46459205:

The registrant briefly summarizes product performance data from MRIDs 46459206 and 46459207. A brief summary is also provided of published literature that supports the inhibition of emergence (IE) method to assess efficacy of insect growth regulators (IGRs) and the use of microcosms to determine the efficacy of control agents against mosquitoes. MRID 46459205 also includes a table of relative mosquito species susceptibility to S-methoprene, using *Culex quinquefasciatus* as the standard. Based on test results and the relative efficacy of S-methoprene against different mosquito species, the B2E-07 label application rates are 2.5 to 25 lbs/A (31.78 to 317.80 g a.i./A), depending on the mosquito species, water depth, and organic matter content.

MRID 46459206:

B2E-07 was applied post-hatch at a rate of 2.5 lbs/A to two sites irrigated with sewage effluent and a third site flooded by river water. Mosquito (*Ochlerotatus melanimon*) pupae were collected from the effluent-irrigated sites (average of six inches in depth) and monitored for adult emergence in the laboratory. B2E-07 appeared to inhibit emergence by 100% for three days for treated pupae from both sites, but this could not be confirmed due to a lack of control data. Mosquito (*Anopheles freeborni* and *Culex tarsalis*) larvae collected from the river water site (average of three feet in depth) were monitored in floating screened cages maintained at the site. Development of treated larvae appeared to be delayed, with only 10/40 *Anopheles* larvae and 14/40 *Culex* larvae developing to pupae after nine days, and none of those developing to adults. However, no control data were provided. The river water site test ended prematurely due to water receding from the site.

MRID 46459207:

Outdoor tubs filled with 20 gallons of tap water were treated with B2E-07 applied at rates of 2.5, 5.0, or 7.5 lbs/A. A sentinel cage containing 25 late second instar *Aedes egypti* larvae was situated in each tub at one and at seven days after treatment and monitored for adult emergence. For larvae installed on day 1, B2E-07 at 2.5, 5.0, and 7.5 lbs/A inhibited emergence 39%, 69%, and 69%, respectively, compared to 6% for controls. For larvae installed on day 7, B2E-7 at 2.5, 5.0, and 7.5 lbs/A inhibited emergence by 45%, 85%, and 95%, respectively, compared to 5% for controls. B2E-07 provided the OPPTS recommended level of 95% population reduction only for larvae installed seven days after the 7.5 lbs/A treatment, which exceeds the recommended label application rate of 2.5-5.0 lbs/A for *Aedes*. A similar registered product, Altosid pellets, was used in the same manner of experimentation as a comparison with B2E-07.

cc: A. Gonzales, M. Duggard, BPPD Subject File, IHAD
A. Gonzales, FT, CM2, 08/04/2005

DATA EVALUATION RECORD

ISOPROPYL (2E,4E,7S)-11- METHOXY-3,7,11-TRIMETHYL-2,4-DODECADIENOATE (B2E-07)

STUDY TYPE: **Product Identity and Composition (OPPTS 830.1550)**
Description of Beginning Materials (OPPTS 830.1600)
Description of Formulation Process (OPPTS 830.1650)
Discussion of Formation of Impurities (OPPTS 830.1670)
Preliminary Analysis (OPPTS 830.1700)
Certified Limits (OPPTS 830.1750)
Enforcement Analytical Method (OPPTS 830.1800)
Physical and Chemical Characteristics (OPPTS 830.6302-830.7950)
MRIDs 46459201, 46459202, 46459203, and 46459204

Prepared for
Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37830
Task Order No. 05-011

Primary Reviewer:
John Caton, Ph.D.

Signature: John E Caton
Date: MAY 10 2005

Secondary Reviewers:
Sylvia Milanez, Ph.D., D.A.B.T.

Signature: Sylvia Milanez
Date: MAY 10 2005

Robert H. Ross, M.S., Group Leader

Signature: Robert H Ross
Date: MAY 10 2005

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: L. A. Wilson
Date: MAY 10 2005

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

DATA EVALUATION RECORD

EPA Secondary Reviewer:

STUDY TYPES:	Product Identity and Composition (OPPTS 830.1550) Description of Beginning Materials (OPPTS 830.1600) Description of Formulation Process (OPPTS 830.1650) Discussion of Formation of Impurities (OPPTS 830.1670) Preliminary Analysis (OPPTS 830.1700) Certified Limits (OPPTS 830.1750) Enforcement Analytical Method (OPPTS 830.1800) Physical and Chemical Characteristics (OPPTS 830.6302-830.7950)
MRID NOs:	46459201, 46459202, 46459203, and 46459204
DP BARCODE NO:	314532
CASE NO:	Not found
SUBMISSION NO:	Not found
TEST MATERIAL:	B2E-07 (EPA Reg No. 75318-T; 2.8% isopropyl (2E,4E,7S)-11- methoxy-3,7,11-trimethyl-2,4-dodecadienoate, a.i.)
PROJECT NO:	MRID 46459201: B11/04/0072A; MRID 46459202: B11/04/0072B; MRID 46459203: B09/04/0072C; and MRID 46459204: B11/04/0072D
SPONSOR:	B2E Biotech LLC; 500 Mamaroneck Ave., Harrison, NY 10528
TESTING FACILITY:	B2E Biotech LLC; 500 Mamaroneck Ave., Harrison, NY 10528
TITLES OF REPORTS:	MRID 46459201: Product Identity and Composition - B2E-07; MRID 46459202: Description of Materials Used to Produce the Product - B2E-07; MRID 46459203: Description of the Formulation Process - B2E-07; and MRID 46459204: Certified Limits B2E-07
AUTHOR:	William K Mintz
STUDY COMPLETED:	November 13, 2004 (MRIDs 46459201, 46459202, 46459204); September 10, 2004 (MRID 46459203)

GOOD LABORATORY PRACTICE: Information in MRIDs 46459201, 46459202, 46459203, and 46459204 is not subject to GLP standards.

CONCLUSION: B2E-07 is an EP intended to be used to prevent the emergence of adult mosquitoes. The active ingredient is 2.800% w/w isopropyl (2E,4E,7S)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate (source material is [redacted] The inerts are [redacted] The beginning materials were adequately presented and the certified limits were within OPPTS 830.1750 guidelines. The formulation process description did not explain [redacted], and the amounts of several ingredients were not consistent with the amounts specified on the CSF. No chemical reactions occur and no new impurities are formed during the manufacturing process. Preliminary analysis and enforcement analysis are not required. Physical/chemical properties were self-certified and are adequate.

CLASSIFICATION: **ACCEPTABLE**, pending (1) an explanation on how [redacted] (2) reconciling the differences in quantities of [redacted] specified on the CSF compared to the quantities used in the formulation process; (3) correctly spelling [redacted] on the CSF and (4) correcting the CAS No. for [redacted] on the CSF.

~~*CONTAINS CONFIDENTIAL BUSINESS INFORMATION*~~

Test Materials: B2E-07 containing 2.8% isopropyl (2E,4E,7S)-11- methoxy-3,7,11-trimethyl-2,4-dodecadienoate as a.i.

I. **PRODUCT IDENTITY AND COMPOSITION:** B2E-07 (EPA Reg. No. 75318-T) is an end-use product (EP) that functions as an insect growth regulator to prevent the emergence of adult mosquitoes. The active ingredient is 2.800% w/w isopropyl (2E,4E,7S)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate (CAS No. 65733-16-6, PC code 105402). The source material is [redacted] CAS No. 40596-69-8, PC code 105401) which contains the active ingredient at [redacted] purity. The inert ingredients are [redacted]

[redacted]

Deficiencies: The CAS Number for [redacted] should be corrected and [redacted] is spelled incorrectly on the CSF.

II. **DESCRIPTION OF BEGINNING MATERIALS:** [redacted]

Deficiencies: None

III. **DESCRIPTION OF PRODUCTION PROCESS:** [redacted]

Reviewer Note: [redacted]

Deficiencies: *The differences in quantities specified on the CSF and the quantities used in* the formulation process must be reconciled.

IV. **DISCUSSION OF FORMATION OF IMPURITIES:** No chemical reactions occur during the batch formulation process ; therefore, no new impurities will be produced. Any impurities present in the formulated end use product would have been carried over from the starting materials. The chemical purity of the starting materials ranges from [redacted] Accordingly, any individual impurity associated with a starting material should be present at <0.10% in the final product.

Deficiencies: None.

V. **PRELIMINARY ANALYSIS:** Preliminary analysis was not conducted and is not necessary because the EP is made using a registered [redacted] isopropyl (2E,4E,7S)-11- methoxy-3,7,11-trimethyl-2,4-dodecadienoate)

Deficiencies: None.

VI. **CERTIFIED LIMITS:** B2E07 contains 2.800% by weight (limits of 2.660-2.940%) isopropyl (2E,4E,7S)-11- methoxy-3,7,11-trimethyl-2,4-dodecadienoate, active ingredient. The lower and upper certified limits for the inert ingredients are listed in Table 1. All certified limits listed on the CSF and in MRID 46459204 are within the guidelines proposed in OPPTS 830.1750. However, the weights for [redacted] of product in the description of the formulation process (MRID 46459203, page 4 of Confidential Attachment). If the amounts of these inerts are altered in the product upon reconciling these discrepancies, the certified limits need to be adjusted accordingly to remain within OPPTS 830.1750 guidelines.

Deficiencies: None. [If the weights for [redacted] are altered upon reconciling discrepancies between the CSF and MRID 46459203, the certified limits need to be adjusted accordingly to remain within OPPTS 830.1750 guidelines.]

TABLE 1. Nominal concentrations and the upper and lower limits for the ingredients of B2E-07[a]

Ingredient	PC Code	Nominal	Lower limit	Upper limit
		% by weight		
Active ingredient				
[redacted] isopropyl (2E,4E,7S)-11- methoxy-3,7,11-trimethyl-2,4-dodecadienoate, active ingredient (CAS No. 65733-16-6, P C Code 105402)	105402	2.800 as a.i.	2.660% as a.i.	2.940% as a.i.
Inert ingredients				
[redacted]				
Total	--	100%	--	--

[a] Data from CSF and from MRID 46459204 (p. 3, Confidential Attachment).

VII. **ENFORCEMENT ANALYTICAL METHOD:** The active ingredient was determined in the TGAI and in the finished end use product by gas chromatography and HPLC. Because the EP is made using a registered TGAI/MP, this guideline does not need to be addressed.

Deficiencies: None.

VIII. **PHYSICAL AND CHEMICAL CHARACTERISTICS:** Self-certified.

TABLE 2. Physical and chemical properties		
Guideline Reference No./Property	**Description of Result**	**Methods/ Source of data**
830.6302 Color	Black	
830.6303 Physical State	Granule	
830.6304 Odor	Almost none	
830.6313 Stability	Not required for EP	
830.6314 Oxidation/Reduction: Chemical Incompatibility	The material is not reactive nor does it contain an oxidizing or reducing agent	
830.6315 Flammability	The product does not contain a combustible liquid	CSF
830.6316 Explodability	The product is not potentially explosive based on structure	
830.6317 Storage Stability	There has been no change in the concentration of the AI under ambient conditions or under accelerated shelf conditions for 30 days in a multi-wall paper bag.	
830.6319 Miscibility	Not applicable for solid	
830.6320 Corrosion Characteristics	There have been no observations of reactivity of the granules or the multi-wall paper bag after 30 days in ambient conditions or under accelerated shelf life conditions.	
830.6321 Dielectric Breakdown Voltage	Not applicable for solid	
830.7000 pH	Not required	CSF
830.7050 UV/Visible	Not required for EP	
830.7100 Viscosity	Not applicable for solid	
830.7200 Melting Range	Not required for EP	
830.7220 Boiling Range	Not required for EP	
830.7300 Bulk Density	89.9 lbs/ft^3	CSF
830.7370 Dissociation Constant in Water	Not required for EP	
830.7520 Particle Size/Distribution	[redacted]	MRID 46459208
830.7550 Partition Coefficient	Not required for EP	
830.7840 Water Solubility	Not required for EP	
830.7950 Vapor Pressure	Not required for EP	

IX. ADDITIONAL REVIEWER'S COMMENTS: None

DATA EVALUATION RECORD

ISOPROPYL (2E,4E,7S)-11-METHOXY-3,7,11-TRIMETHYL-2,4-DODECADIENOATE (B2E-07)

STUDY TYPE: Product Performance Summary and Bridging Data (Nonguideline)

MRID 46459205

Prepared for
Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1801 Bell Street
Arlington, VA 22202

Prepared by
Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37830
Task Order No. 05-011

Primary Reviewer:
Eric B. Lewis, M.S.

Signature: Eric B. Lewis
Date: MAY 10 2005

Secondary Reviewers:
Anthony Q. Armstrong, M.S.

Signature:
Date: MAY 10 2005

Robert H. Ross, M.S., Group Leader

Signature:
Date: MAY 10 2005

Quality Assurance:
Lee Ann Wilson, M.A.

Signature:
Date: MAY 10 2005

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DATA EVALUATION RECORD

EPA Secondary Reviewer:

STUDY TYPE:	Product Performance Summary and Bridging Data (Nonguideline)
MRID NO:	46459205
SUBMISSION NO:	Not provided
DP BARCODE:	DP314532
TEST MATERIAL:	B2E-07 [isopropyl (2E,4E,7S)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate, 2.8%]
PROJECT STUDY NO:	B11/04/0073A
SPONSOR:	B2E Biotech LLC, 500 Mamaroneck Ave., Harrison, NY 10528
TESTING FACILITY:	NA
TITLE OF REPORT:	B2E-07 Product Performance Summary and Bridging Data
AUTHOR:	Mintz, W.K.
STUDY COMPLETED:	November13, 2004
GOOD LABORATORY PRACTICE:	A signed and dated GLP statement was provided. The study was not subject to GLP standards.
CONCLUSION:	MRID 46459205 briefly summarizes product performance data from MRIDs 46459206 and 46459207. It also briefly summarizes published literature that supports the inhibition of emergence (IE) method to assess efficacy of insect growth regulators (IGRs) and the use of microcosms to determine the efficacy of control agents against mosquitoes. MRID 46459205 also includes a table of relative mosquito species susceptibility to S-methoprene, using *Culex quinquefasciatus* as the standard. Based on test results and the relative efficacy of S-methoprene against different mosquito species, the B2E-07 label application rates are 2.5 to 25 lbs/A (31.78 to 317.80 g a.i./A), depending on the mosquito species, water depth, and organic matter content.
CLASSIFICATION:	Supplemental

~~CONTAINS CONFIDENTIAL BUSINESS INFORMATION~~

Test Material

B2E-07 is an end use product applied either pre- or post-hatch to mosquito breeding sites to prevent emergence of adults. The active ingredient is 2.8% by weight S-methoprene [isopropyl (2E,4E,7S)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate].

Product Performance Data

MRID 46459205 briefly summarizes product performance data from two of the registrant's submissions (MRIDs 46459206 and 46459207). It also briefly summarizes published literature

that supports the inhibition of emergence (IE) method to assess efficacy of insect growth regulators (IGRs) and the use of microcosms to determine the efficacy of control agents against mosquitoes. MRID 46459205 also includes a table of relative mosquito species susceptibility to S-methoprene, using *Culex quinquefasciatus* as the standard.

The test evaluated in MRID 46459206 was conducted during August, 2004, in Owens Valley, CA. B2E-07 granules were hand-applied to two irrigated pastures containing *Ochlerotatus melanimon* mosquitoes and one oxbow river slough containing *Anopheles freborni* and *Culex tarsalis* mosquitoes. The summary in MRID 46459205 states that B2E-7 achieved complete (100%) inhibition of adult emergence of all three mosquito species at the treated sites (the reviewer found the study to be unacceptable, since no control data were provided).

The test evaluated in MRID 46459207 was conducted during October and November, 2004, in Riverside, CA. B2E-07 was applied at rates of 2.5, 5.0, or 7.5 lbs/A to 4.36 ft^2 microcosms. No results were presented in the summary provided in MRID 46459205 (the reviewer found the study to be unacceptable, since the only application rate that achieved the OPPTS-recommended 95% minimum reduction in larval population exceeded the recommended application rate on the product label).

Methodology

The study author states that inhibition of emergence has become the standard for evaluating IGR larvacides and provides citations to three published articles that describe the procedures used to assess the efficacy of S-methoprene in MRIDs 46459206 and 46459207. Copies of these references were not provided in MRID 46459205.

Microcosms have evolved to be a precise method to study the impact of materials used for mosquito control. Microcosms are used rather than field tests because they overcome the problems associated with field site variability, are highly reproducible, and allow dependable statistical analysis of the test data. Microcosms also allow similar test conditions (i.e., identical nutrient levels, water quality, depth, temperature); precise administration of treatment doses; and comparison of treatments with untreated controls.

Bridging Data

The controlled release formulation technology for S-methoprene was developed for use in Altosid XR-G (EPA Reg. No. 2724-451), and a similar controlled release technology is used in B2E-07. The unique feature of this technology is the ability to achieve a flat line release of S-methoprene. Since the formulation technology used in B2E-07 limits the daily release rate of active ingredient, the length of control is determined by the dosage rate applied. A chart demonstrating the relationship between application rate and days of control is provided on p. 7 of MRID 46496205. The chart indicates that B2E-07 dosage rates of 2.5 to 10.0 lbs/A provide control for 21 to 80 days, respectively, providing an average release rate of 1.59 g a.i./day.

Study Author's Conclusion

The study author concluded that B2E-07 label application rates were established by test results and mosquito susceptibility data showing that various mosquito species are from 1.5 to 294.1 times more susceptible to S-methoprene than *Culex quinquefasciatus*. Other factors to be considered are weather conditions, water quality and quantity, product formulation, and dosage rates. The label dosage rates range from 2.5 to 25 lbs/A (31.78 to 317.80 g a.i./A) for different

formulations of B2E-07. The lower rates are for application to floodwater mosquitoes (*Aedes, Ochlerotatus, Psorophora*) and *Anopheles* in shallow water (<2 ft) with minimal vegetation and/or organic matter. The higher rates are for semi-permanent water mosquitoes *(Culex, Culiseta, Coquillettidia, Mansonia*) in deeper water (>2 ft) with heavy vegetation and/or higher organic matter.

The study author also concluded that the scientific literature demonstrates that inhibition of emergence is only one of many control mechanisms of S-methoprene on immature mosquito populations.

Reviewer's Comments

The reviewer notes that the product performance studies summarized in MRID 46459205 were judged to be unacceptable. Also, page 6 of MRID 46459205 states that a review of the literature on sub-lethal treatment effects of S-methoprene on mosquitoes is included in the document, but the reviewer could not find it.

DATA EVALUATION RECORD

ISOPROPYL (2E,4E,7S)-11-METHOXY-3,7,11-TRIMETHYL-2,4-DODECADIENOATE (B2E-07)

STUDY TYPE: Product Performance (OPPTS 810.3400)

MRID 46459206

Prepared for
Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1801 Bell Street
Arlington, VA 22202

Prepared by
Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37830
Task Order No. 05-011

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DATA EVALUATION RECORD

EPA Secondary Reviewer:

STUDY TYPE:	Product Performance (810.3400)
MRID NO:	46459206
DP BARCODE:	DP314532
CASE NO:	Not provided
SUBMISSION NO:	Not provided
TEST MATERIAL:	B2E-07 [isopropyl (2E,4E,7S)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate, 2.8%]
STUDY NO:	S11-04-0073B
SPONSOR:	B2E Biotech LLC, 500 Mamaroneck Ave., Harrison, NY 10528
TESTING FACILITY:	B2E Biotech LLC, 500 Mamaroneck Ave., Harrison, NY 10528
TITLE OF REPORT:	Assessment of B2E-07 with Mosquito Larvae
AUTHOR:	Mintz, W.K.
STUDY COMPLETED:	November 13, 2004
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	A signed GLP statement was provided. The study was GLP compliant with the following exceptions: 1) there was no quality assurance audit; 2) the stability, characterization, identity, and verification of the test substance concentration as received and tested was the responsibility of the study sponsor; 3) signatures of individual research assistants were not obtained, and 4) B2E Biotech will archive all signed reports and protocols.

STUDY SUMMARY:	B2E-07 (active ingredient, 2.8% by weight S-methoprene) was applied post-hatch at a rate of 2.5 lbs/A to two sites irrigated with sewage effluent and a third site flooded by river water. Mosquito (*Ochlerotatus melanimon*) pupae were collected from the effluent-irrigated sites and monitored for adult emergence in the laboratory. B2E-07 appeared to inhibit emergence by 100% for three days for treated pupae from both sites, but this could not be confirmed due to a lack of control data. Mosquito (*Anopheles freeborni* and *Culex tarsalis*) larvae collected from the river water site were monitored in floating screened cages maintained at the site. Development of treated larvae appeared to be delayed, with only 10/40 *Anopheles* larvae and 14/40 *Culex* larvae developing to pupae after nine days, and none of those developing to adults. However, no control data were provided. The river water site test ended prematurely due to water receding from the site.
CLASSIFICATION:	UNACCEPTABLE, but upgradable if acceptable control data are provided.

Test Material

B2E-07 2.8% S-Methoprene [redacted] (no batch number provided) is an end use product applied either pre- or post-hatch to breeding sites to prevent emergence of adult mosquitoes. The active ingredient is 2.8% by weight S-methoprene [isopropyl (2E,4E,7S)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate].

Test Methods

The study was conducted between August 15 and August 31, 2004, in the Owens Valley of California. The test sites were a 0.25 A irrigated pasture, a 0.08 A irrigated swale, and a 0.31 A Owens River oxbow slough. The pasture and swale sites were irrigated with highly organic sewage effluent to an average depth of six inches. The slough was naturally flooded by river water to an average depth of three feet. The test mosquitoes were natural populations that hatched following flooding of the sites: *Ochlerotatus melanimon* at the pasture and swale sites and *Anopheles freeborni* and *Culex tarsalis* at the slough site.

B2E-07 was hand-broadcasted post-hatch at all three sites at a treatment rate of 2.5 lbs/A. At the pasture and swale sites, 40 free-swimming pupae were collected around the perimeter of each site, placed in containers with lids, and transferred to the laboratory. Adult emergence of these pupae was assessed twice weekly by counting and removing the dead pupae, dead adults, and live adults in each container. At the slough site, 40 late third and early fourth instar larvae of each species were collected and placed into separate screened, floating containers that remained at the test site.

Results Summary

For larvae collected at the pasture and swale sites, adult emergence of the treated pupae was 100% inhibited. At the slough site, development of treated larvae was delayed, with only 10 *Anopheles* larvae and 14 *Culex* larvae developing to pupae after nine days. All 24 of those pupae died. A drop in the river level dried out the site before any of the remaining larvae developed to pupae.

Study Author's Conclusions

The study author concluded that B2E-07 applied post-hatch at 2.5 lbs/A achieved 100% inhibition of emergence of all pupae.

Reviewer's Comments

This study is not acceptable because control data were not provided, and therefore results of the experiments could not be validated.

If acceptable control data had been submitted, the following comments apply:

1a. The submitted data demonstrate efficacy by means of percent inhibition of emergence (I.E.) of Ochlerotatus melanimon (pre- or post-hatch) at 2.5 pounds/acre (lbs/A) in sites with an average water depth of six inches for up to three days.

1b. Temperatures greater than 90°F were recorded at the site testing the EP against Anopheles freeborni and Culex tarsalis, which also dried out during the study. The registrant claims 100% I.E. at the sites, explaining that delayed development time is a secondary effect of (S)-Methoprene, therefore the larvae died by drying out before developing into pupae, and those that did develop died in the pupal stage. This cannot be verified without control data. If verified with control data, the submitted data demonstrate efficacy for the two species at 2.5 lbs/A with an average water depth of three feet for up to nine days.

2. Based on the experimental data (MRID 46459206) and data from literature submitted (MRID 46459205), it can be concluded that the EP is efficacious in controlling mosquito populations for up to nine days at indicated label rates. However, the length of control is not in accordance with label claims. Label rates currently establish control 30 to 80 days, depending on species of mosquito and application rate.

DATA EVALUATION RECORD

ISOPROPYL (2E,4E,7S)-11-METHOXY-3,7,11-TRIMETHYL-2,4-DODECADIENOATE (B2E-07)

STUDY TYPE: Product Performance (OPPTS 810.3400)

MRID 46459207

Prepared for
Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1801 Bell Street
Arlington, VA 22202

Prepared by
Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37830
Task Order No. 05-011

Primary Reviewer:
Eric B. Lewis, M.S.

Signature: Eric B. Lewis
Date: MAY 10 2005

Secondary Reviewers:
Anthony Q. Armstrong, M.S.

Signature:
Date: MAY 10 2005

Robert H. Ross, M.S., Group Leader

Signature:
Date: MAY 10 2005

Quality Assurance:
Lee Ann Wilson, M.A.

Signature:
Date: MAY 10 2005

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

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DATA EVALUATION RECORD

EPA Secondary Reviewer:

STUDY TYPE:	Product Performance (810.3400)
MRID NO:	46459207
DP BARCODE:	DP314532
CASE NO:	Not provided
SUBMISSION NO:	Not provided
TEST MATERIAL:	B2E-07 [isopropyl (2E,4E,7S)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate, 2.8%]
STUDY NO:	S11-04-0073C
SPONSOR:	B2E Biotech LLC, 500 Mamaroneck Ave., Harrison, NY 10528
TESTING FACILITY:	B2E Biotech LLC, 500 Mamaroneck Ave., Harrison, NY 10528
TITLE OF REPORT:	Assessment of B2E-07 and Altosid Pellets with Mosquito Larvae
AUTHOR:	Mintz, W.K.
STUDY COMPLETED:	November 13, 2004
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	A signed GLP statement was provided. The study was GLP compliant with the following exceptions: 1) there was no quality assurance audit; 2) the stability, characterization, identity, and verification of the test substance concentration as received and tested was the responsibility of the study sponsor; 3) signatures of individual research assistants were not obtained, and 4) B2E Biotech will archive all signed reports and protocols.

STUDY SUMMARY:	Outdoor tubs filled with 20 gallons of tap water were treated with B2E-07 applied at rates of 2.5, 5.0, or 7.5 lbs/A. A sentinel cage containing 25 late second instar *Aedes egypti* larvae was situated in each tub at one and at seven days after treatment and monitored for adult emergence. For larvae installed on day 1, B2E-07 at 2.5, 5.0, and 7.5 lbs/A inhibited emergence 39%, 69%, and 69%, respectively, compared to 6% for controls. For larvae installed on day 7, B2E-7 at 2.5, 5.0, and 7.5 lbs/A inhibited emergence by 45%, 85%, and 95%, respectively, compared to 5% for controls. B2E-07 provided the OPPTS recommended level of 95% population reduction only for larvae installed seven days after the 7.5 lbs/A treatment, which exceeds the recommended label application rate of 2.5-5.0 lbs/A for Aedes. A similar registered product, Altosid pellets, was used in the same manner of experimentation as a comparison with B2E-07.
CLASSIFICATION:	UNACCEPTABLE, upgradable.

Test Material

B2E-07 2.8% S-Methoprene [redacted], lot number I-10-6-04. B2E-07 is an end use product applied either pre- or post-hatch to breeding sites to prevent emergence of adult mosquitoes. The active ingredient is 2.8% by weight S-methoprene [isopropyl (2E,4E,7S)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate].

Test Methods

The study was conducted in plastic tubs located outdoors with trees and other vegetation in Riverside, CA. The tubs were 18 inches deep with a surface area of 4.36 ft^2. Prior to flooding, each tub was enriched with 10 g of rabbit pellets. Tubs were flooded on October 12, 2004, with 20 gallons of tap water, and volume was kept relatively constant by weekly addition of water. At flooding, a min-max thermometer was installed in one tub to monitor temperature during the test.

The tubs were treated the day after flooding. Treatments indlcuded B2E-07 applied at rates of 2.5, 5.0, and 7.5 lbs/A, and a comparison treatment of Altosid pellets (lot number 031216168, EPA Reg. No. 2724-448) applied at the same active ingredient rate as that for B2E-07 at 5.0 lbs/A (Table 1). An untreated control was also included. All four treatments and the control were replicated four times in a random design.

On the day of treatment, a sentinel cage containing 25 late second instar *Aedes egypti* larvae was installed in each tub. An additional cage of larvae was placed in each tub on day seven post-treatment. Adult emergence was evaluated by counting and removing dead larvae, dead pupae, and pupal exuviae twice a week until all pupae had emerged or died. Results were expressed as a percent inhibition of emergence (%IE).

Results Summary

Results are presented in Table 1. In the initial cohort of larvae, development time from introduction to adult emergence or pupal/adult death was 15 days. B2E-07 at 2.5, 5.0, and 7.5 lbs/A inhibited emergence by 39%, 69%, and 69%, respectively, compared to 6% for controls. In the cohort installed on day 7, the development time from introduction to adult emergence or pupal/adult death was 16 days. B2E-7 at 2.5, 5.0, and 7.5 lbs/A inhibited emergence by 45%, 85%, and 95%, respectively, compared to 5% for controls. B2E-07 applied at 5.0 lbs/A was more effective than Altosid applied at 3.3 lbs/A, which was an approximately equal application of a.i./A.

Table 1. Effect of B2E-07 on percent emergence of Aedes spp. mosquitoes

Treatment	Application rate	Inhibition of emergence (%IE)	
		Larvae installed on day 0 (cohort 1)	Larvae installed on day 7 (cohort 2)
Control	NA	6	5
B2E-07	2.5 lbs/A (31.78 g a.i./A)	39	45
	5.0 lbs/A (63.56 g a.i./A)	69	85
	7.5 lbs/A (95.34 g a.i./A)	69	95
Altosid pellets	3.3 lbs/A (63.67 g a.i./A)	46	85

Data taken from pp. 5-6, MRID 46459207

Study Author's Conclusions

The study author concluded that: 1) for the first cohort, all the treatments provided good control, and B2E-07 was more effective than Altosid pellets at a comparable active ingredient level; 2) for the second cohort, all treatments except B2E-07 at 2.5 lbs/A provided significantly more control than was seen for the first cohort, indicating accumulation of S-methoprene in the water as a result of further release from the previously-applied granules; and 3) for the second cohort, B2E-07 at 5 lbs/A was as effective as Altosid pellets at a comparable active ingredient level, and B2E-07 at 7.5 lbs/A was more effective than Altosid at 3.3 lbs/A.

Reviewer's Comments

The reviewer agrees that all the B2E-07 treatments inhibited mosquito emergence compared to controls, and that B2E-07 provided equivalent or better control than Altosid pellets that were applied at a comparable active ingredient level. However, OPPTS 810.3400 recommends a minimum of 95% population reduction for mosquito larvae. B2E-07 provided this level of reduction only for the second cohort in the 7.5 lbs/A treatment. The reviewer notes that the 7.5 lbs/A application rate exceeds the recommended application rate of 2.5 to 5.0 lbs/A for *Aedes*

given on the "regular" B2E-07 label, but falls within the rate range recommended on the Aquaprene Flex Granules label. The product label claims B2E-07 prevents emergence for up to 40 days; this could not be verified, since the study was terminated after the first two cohorts due to failed egg hatch and low water temperature.

DATA EVALUATION RECORD

ISOPROPYL (2E,4E,7S)-11-METHOXY-3,7,11-TRIMETHYL-2,4-DODECADIENOATE (B2E-07)

STUDY TYPE: Request for Mammalian Toxicity Waivers

Acute Oral Toxicity	**OPPTS 870.1100**
Acute Dermal Toxicity	**OPPTS 870.1200**
Acute Inhalation Toxicity	**OPPTS 870.1300**
Primary Eye Irritation	**OPPTS 870.2400**
Primary Dermal Irritation	**OPPTS 870.2500**
Dermal Sensitization	**OPPTS 870.2600**

MRID 46459208

Prepared for
Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1801 Bell Street
Arlington, VA 22202

Prepared by
Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37830
Task Order No. 05-011

Primary Reviewer:
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Signature: Eric B. Lewis
Date: MAY 10 2005

Secondary Reviewers:
Sylvia Milanez, Ph.D., D.A.B.T.

Signature: Sylvia Milanez
Date: MAY 10 2005

Robert H. Ross, M.S., Group Leader

Signature: Robert H. Ross
Date:

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: L.A. Wilson
Date: MAY 10 2005

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

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DATA EVALUATION RECORD

EPA Secondary Reviewer:

STUDY TYPE:	Waiver request for mammalian toxicity data (nonguideline)
MRID NO:	46459208
DP BARCODE:	DP314532
CASE NO:	Not provided
SUBMISSION NO:	Not provided
TEST MATERIAL:	B2E-07 [isopropyl (2E,4E,7S)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate, 2.8%]
STUDY NO:	NA
SPONSOR:	B2E Biotech LLC. 500 Mamaroneck Ave., Harrison, NY 10528
TESTING FACILITY:	B2E Biotech LLC. 500 Mamaroneck Ave., Harrison, NY 10528
TITLE OF REPORT:	Response to Tier I Biochemical Pesticide Data Requirements for B2E-07
AUTHOR:	Mileson, B.E.
STUDY COMPLETED:	January 24, 2005
CONFIDENTIALITY CLAIMS:	None
GOOD LABORATORY PRACTICE:	A signed GLP statement was provided. The study was not GLP compliant. No quality assurance unit was in place, and no study director was assigned.

STUDY SUMMARY: The registrant requested waivers for mammalian toxicity testing requirements. Acute toxicity studies submitted for the [redacted] supported placement in Toxicity Category IV for each of the six-pack data requirements. The inert ingredients in B2E-07 are either on EPA List 4A or 4B, are regarded as GRAS by U.S. FDA, or are not of toxicological concern. [redacted] potential to have toxic/irritant respiratory effects, but in the EP, it is bound in a granular form which is not respirable. The registrant must clarify if all respirable particles are removed from the EP during the manufacturing process, and address the durability of the granules as to whether they may break apart easily during packaging, storage and use, which could possibly result in exposure to fine grains and their potential irritant effects. With the exception of [redacted] low concentrations of the inerts in the formulation are not expected to have irritant effects.

CLASSIFICATION: ACCEPTABLE, pending submission of requested information.

Test Material

B2E-07 2.8% S-Methoprene [redacted]. B2E-07 is an end use product applied either pre- or post-hatch to breeding sites to prevent emergence of adult mosquitoes. The active ingredient is 2.8% by weight S-methoprene [isopropyl (2E,4E,7S)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate].

Waiver Requests

The registrant is requesting a waiver of data requirements for the following OPPTS guidelines:

Acute Oral Toxicity	OPPTS 870.1100
Acute Dermal Toxicity	OPPTS 870.1200
Acute Inhalation Toxicity	OPPTS 870.1300
Primary Eye Irritation	OPPTS 870.2400
Primary Dermal Irritation	OPPTS 870.2500
Dermal Sensitization	OPPTS 870.2600

Rationale

[redacted]

[redacted]

Approximately [redacted] which is not of toxicological concern. The other inerts are [redacted].

Reviewer's Comments

The registrant must clarify if all respirable particles are removed from the EP during the manufacturing process, and address the durability of the granules as to whether they may break apart easily during packaging, storage and use, which could possibly result in exposure to fine grains and their potential irritant effects.

13544

R142674

Chemical: S-Methoprene

PC Code:
105402

HED File Code: 41500 BPPD Tox/Chem
Memo Date: 8/4/2005
File ID: DPD314532
Accession #: 000-00-9002

HED Records Reference Center
5/2/2007